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THYROTROPIN-RELEASING HORMONE ANALOGS IN CNS INJURY

BACKGROUND OF THE INVENTION

Thyrotropin-releasing hormone (TRH), L-pyroglutamyl-L-histidyl-L-prolineamide, has been found in the spinal cord and has been found to have a variety of effects on the central nervous system. For example, TRH has potent excitatory effects in the spinal cord, thereby increasing neuronal activity and enhancing monosynaptic and polysynaptic reflexes.

TRH improves long-term neurologic outcome following experimental spinal trauma. Consequently, L-pyro-2-aminoadipyl-histidyl-thiazolidine-4-carboxamide and orotyl-L-histidyl-L-prolineamide, synthetic analogs thereof, were studied for such activity in Faden et al., Neurology, Vol. 35, pp. 1331-1334 (1985).

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating traumatic central nervous system injury in a patent suffering from brain or spinal cord trauma which comprises administering to said patient an effective amount of a thyrotropin-releasing hormone analog having preservation of carboxy-terminal prolineamide moiety. The TRH analog of the present invention can also be any analog which modifies the pyroglutamyl moiety so as to prevent enzyme degradation or increase CNS potency. Exemplary modifications include replacement of the pyrrolidinone residue with other rings. These new rings preferably contain the moiety O=C-NH-C-.

Fluorinated histidyl analogs are also contemplated by the present invention. Exemplary of such analogs are 2-fluoro and 4-fluoro histidyl TRH analogs. These analogs can be prepared through the fluorination of TRH by conventional techniques.

Iodinated TRH analogs, preferably 2,4-diodo-(Im)-TRH analogs are additionally contemplated in the present invention. Preferably, said thyrotropin-releasing hormone

analog is selected from the group comprising 6-methyl-5-oxo-thiomorpholinyl-3-carbonyl-histidyl-prolineamide, 4-(2-oxo-trimethylenimine)-carbonyl-histidyl-prolineamide, and 4-(2-oxo-furan)-carbonyl-histidyl-prolineamide.

As an effective amount of the thyrotropin-releasing hormone analog of the present invention there is contemplated an amount of analog substantially higher than that required to induce maximal thyrotropin-releasing hormone activity. An effective amount of the thyrotropin-releasing hormone analog of the present invention is from about 0.2 to about 2 mg/kg body weight of the patient administered 2-4 times during the first 48 hours after trauma, 1-2 times daily thereafter. A preferred embodiment of the present invention involves an effective amount of the hormone analog from about 0.2 to 1 mg/kg body weight of the patient administered within 24 hours of trauma by 2-4 intravenous or intramuscular injections over 24 hours.

The thyrotropin-releasing hormone analog of the present invention may be administered to the patient in any dosage form convenient under the patient's specific circumstances. Usually, parenteral administration is preferred.

As a parenteral dosage form there is contemplated a dosage unit suitable for intravenous administration which comprises (i) an effective amount of a thyrotropin-releasing hormone analog having an unmodified carboxy terminus and (ii) a pharmaceutically acceptable solution.

As a pharmaceutically acceptable solution there is contemplated any solution which is safe for injection and which is biologically inert and hence does not interfere with the active ingredient. As such a pharmaceutically acceptable solution may include an isotonic solution suitable for injection into a patient. The isotonic solution may contain water, salt and conventional ingredients such as glucose.

Such a pharmaceutically acceptable solution may contain purified water admixed with preservatives, flavors, colorants, flavor enhancing agents and other excipients. Exemplary of such additives are sodium benzoate, methyl paraben, propylene glycol, glycerin, sorbitol, alcohol, sucrose, saccharin, menthol and citric acid.

A preferred embodiment of the present invention provides a method of treating traumatic central nervous system injury in a patient suffering from brain or spinal trauma through administration of a thyrotropin-releasing hormone analog which is 6-methyl-5-oxo-thiomorpholinyl-3-carbonyl-histidyl-prolineamide. 6-Methyl-5-oxo-thiomorpholinyl-3-carbonyl-histidyl-prolineamide. 4-(2-Oxo-trimethylenimine)-carbonyl-histidyl-prolineamide may be obtained through Chemie Grünenthal.

Another preferred embodiment of the present invention provides a method of treating traumatic central nervous system injury in a patient suffering from brain or spinal trauma through administration of a thyrotropin-releasing hormone analog which is 4-(2-oxo-trimethylenimide)-carbonyl-histidyl-prolineamide may be obtained through Dow Chemical Company.

A preferred embodiment of the present invention provides a method of treating traumatic central nervous system injury in a patient suffering from brain or spinal trauma through administration of a thyrotropin-releasing hormone analog which is 4-(2-oxo-furan)-carbonyl-histidyl-prolineamide. 4-(2-Oxo-furan)-carbonyl-histidyl-prolineamide may be obtained through Yamanouchi Pharmaceutical Co., Ltd.

An additional embodiment of the present invention provides a method of treating traumatic central nervous system injury in a patient, wherein a thyrotropin-releasing hormone analog is administered in a dosage of from about

0.2 to about 2 mg/kg 2-4 times daily. A more preferred embodiment involves a method, wherein a thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 1 mg/kg 2 times daily.

The following illustrate the invention.

EXAMPLE 1

6-Methyl-5-oxy-thiomorpholinyl-3-carbonyl-histidyl-prolineamide is admixed with 15 cc isotonic solution to obtain a final concentration of active ingredient in the solution of 5 mg/cc.

EXAMPLE 2

4-(2-Oxo-trimethylenimine)-carbonyl-histidyl-prolineamide is admixed with 15 cc isotonic solution to obtain a final concentration of active ingredient in the solution of 10 mg/cc.

EXAMPLE 3

4-(2-Oxo-furan)-carbonyl-histidyl-prolineamide is admixed with 12.5 cc isotonic solution to obtain a final concentration of active ingredient in the solution of 7.5 mg/cc.

EXAMPLE 4

Induction of tissue protective activity in a patient suffering from traumatic central nervous system injury is accomplished through injection of 10 cc of the pharmaceutical preparation of Example 1 2 times daily for 1 day.

EXAMPLE 5

Induction of tissue protective activity in a patient suffering from traumatic central nervous system injury is accomplished through injection of 15 cc of the pharmaceutical preparation of Example 2 4 times daily for 2 days.

EXAMPLE 6

Induction of tissue protective activity in a patient suffering from traumatic central nervous system injury is accomplished through injection of 10 cc of the pharmaceutical preparation of Example 3 2 times daily for 30 days.

WHAT IS CLAIMED IS:

1. A method of treating traumatic central nervous system injury in a patient suffering from brain or spinal cord trauma which comprises administering to said patient an effective amount of a thyrotropin-releasing hormone analog having preservation of the terminal prolineamide moiety.

2. A method of claim 1, wherein said thyrotropin-releasing hormone analog is 6-methyl-5-oxo-thiomorpholinyl-3-carbonyl-histidyl-prolineamide.

3. A method of claim 1, wherein said thyrotropin-releasing hormone analog is 4-(2-oxo-trimethylenimine)-carbonyl-histidyl-prolineamide.

4. A method of claim 1, wherein said thyrotropin-releasing hormone analog is 4-(2-oxo-furan)-carbonyl-histidyl-prolineamide.

5. A method of claim 1, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 2 times daily.

6. A method of claim 1, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 4 times daily.

7. A method of treating traumatic central nervous system injury in a patient suffering from brain or spinal cord trauma which comprises administering to said patient an effective amount of a thyrotropin-releasing hormone analog having a fluorine or iodine substituted histidyl moiety.

8. A method of claim 7, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 2 times daily.

9. A method of claim 7, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 4 times daily.

10. A method of treating traumatic central nervous system injury in a patient suffering from brain or spinal cord trauma which comprises administering to said patient an effective amount of a thyrotropin-releasing hormone analog having a terminal ring containing

O
C-NH-C-.

11. A method of claim 10, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 2 times daily.

12. A method of claim 10, wherein said thyrotropin-releasing hormone analog is administered in a dosage of from about 0.2 to about 2 mg/kg 4 times daily.

PATENT COOPERATION TREATY

DECLARATION OF NON-ESTABLISHMENT OF INTERNATIONAL SEARCH REPORT

issued pursuant to PCT Article 17(2)(a)(1)

IDENTIFICATION OF THE INTERNATIONAL APPLICATION	APPLICANT's OR AGENT's FILE REFERENCE
International Application No. PCT/US 88/01837	International Filing Date 6th June 1988
Receiving Office RO/US	Priority Date Claimed 5th June 1987
Applicant (Name) MEDICIS CORPORATION	

DECLARATION

This International Searching Authority hereby declares that no international search report will be established on the above-identified international application for the reasons indicated below.(1)

1. The subject matter of the international application relates to:(2)

- a. [ ] scientific theories.
- b. [ ] mathematical theories.
- c. [ ] plant varieties.
- d. [ ] animal varieties.
- e. [ ] essentially biological processes for the production of plants and animals, other than microbiological processes and the products of such processes.
- f. [ ] schemes, rules or methods of doing business.
- g. [ ] schemes, rules or methods of performing purely mental acts.
- h. [ ] schemes, rules or methods of playing games.
- i. [X] methods for treatment of the human body by surgery or therapy.
- j. [X] methods for treatment of the animal body by surgery or therapy.
- k. [ ] diagnostic methods.
- l. [ ] mere presentations of information.
- m. [ ] computer programs for which this International Searching Authority is not equipped to search prior art.

2. The failure of the following parts of the international application to comply with prescribed requirements prevents a meaningful search from being carried out:(3)

- a. [ ] the description.
- b. [ ] the claims.
- c. [ ] the drawings.

comment:

CERTIFICATION

International Searching Authority	Date of Mailing	Authorized Officer
ISA / EP	09 NOV 1988	P.C.G. VAN DER PUTTEN

Form PCT/ISA/203 (January 1985)